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Role of Venom-Induced Consumption Coagulopathy in Assessing the Clinical Severity of Soft-Tissue Inflammation and Prognosis in Snakebite Envenomation: A Prospective Observational Study

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Abstract

Aim

The study aims to evaluate the correlation between venom-induced coagulation (VIC) markers and the clinical severity of soft-tissue inflammation and injury in snakebite patients, and to determine the predictive value of these markers for prognosis and the need for intensive medical intervention.

Setting and design

This was a prospective observational study in the emergency department of R.L. Jalappa Hospital and Research Centre, Kolar, Karnataka, South India, over a 12-month period (September 2025-September 2026).

Methods and materials

One hundred twelve adult patients (⩾18 years) presenting within 48 hours of snakebite with localized soft-tissue swelling were enrolled, and soft-tissue involvement was graded as I-IV. Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer were measured at presentation and repeated at 48 hours, with the endpoint being need for “advanced medical intervention.”

Statistical analysis used

Statistical analyses included the Mann-Whitney U test, Spearman correlation, and receiver-operating-characteristic (ROC) analysis with bootstrap-corrected Youden index, Firth penalized logistic regression, and Benjamini-Hochberg correction for multiple comparisons.

Results

Twenty-seven patients (24.1%) had severe local involvement. All five indices differed between the severe and non-severe groups (all $q < 0.001$), but they did not differ between Grades I and II or between Grades III and IV; the association was therefore categorical, not graded. D-dimer separated the two groups completely (maximum non-severe 1,055 ng/mL; minimum severe 1,520 ng/mL). This complete separation is a feature of this sample, so discrimination for severe local involvement could not be validly estimated, and the resulting area under the curve (AUC) of 1.000 should not be interpreted as predictive performance. Advanced intervention was required in 23 of 104 patients (22.1%). For this endpoint, the AUCs were 0.79-0.83 (INR 0.825, 95% confidence interval (CI) 0.70-0.93; D-dimer 0.822, 95% CI 0.71-0.93), negative predictive values were 89.4%-93.6% (lower 95% confidence limits 81%-86%), and no marker was independently predictive in a multivariable model (7.7 events per variable).

Conclusions

Baseline coagulation abnormalities were associated with severe local soft-tissue inflammation/injury and, moderately, with the need for advanced intervention. These are observational associations; they do not show that coagulopathy causes local tissue damage, and unmeasured venom burden may explain both. The grading scale is unvalidated, grading was not blinded to laboratory results, inter-rater reliability was not assessed, and the endpoint is a heterogeneous composite based on 23 events. The findings are hypothesis-generating, and external validation is required before any threshold is used clinically.

Categories: Medical Education, Emergency Medicine, Epidemiology/Public Health
Keywords: d-dimer, prognosis, snakebite envenomation, soft-tissue infection, venom-induced consumption

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coagulopathy

Introduction

Snakebite envenomation is a major public health concern in South India and worldwide, with India among the most heavily affected countries. Each year, it affects approximately 1.8 to 2.7 million people globally and causes an estimated 138,000 deaths. India contributes a large share of this burden, averaging 58,000 deaths annually, highlighting the disproportionate impact relative to other regions, as reported in the study by Gajbhiye et al. [1]. In southern India, snakebites are particularly common and are linked to substantial morbidity and mortality. David et al. [2] reported a 7.5% mortality rate among affected individuals in this region, with acute renal injury and hematotoxic effects identified as key contributors.

Snakebite prevalence in South India is driven by factors including high rural population density, agricultural practices, and the presence of multiple venomous snake species. Most snakebite deaths in India occur in rural areas and outside healthcare facilities [3]. Although healthcare infrastructure has improved over the past two decades, delivering timely prehospital care remains a major obstacle.

Regional snake diversity is wide: a study in Mysore documented 24 species (18 non-venomous, two mildly venomous, and four venomous) [4], and local and systemic effects vary with the species involved. Venom from Viperidae and Crotalidae can induce coagulopathy by disrupting blood coagulation pathways, which may result in disseminated intravascular coagulation (DIC), as described by Mion et al. [5]. Coagulopathy is therefore a critical consideration in clinical management because it can lead to severe hemorrhagic complications, as per Cha et al. [6].

After snakebite, coagulopathy is linked to reduced hematocrit, protein, albumin, and cholesterol levels, along with conditions such as leukocytosis and rhabdomyolysis. The presence of coagulopathy can substantially worsen clinical outcomes in snakebite patients, making careful monitoring and management essential, as mentioned in the Jeon et al. [7] study.

The 20-minute whole blood clotting test (20WBCT) is a traditional diagnostic approach that offers high specificity but variable sensitivity for detecting coagulopathy [8,9]. Local soft-tissue complications of snake envenomation range from venom-induced swelling and inflammation to secondary bacterial infection. Venom cytotoxins injure local tissue, and this injury may predispose to bacterial infection, but swelling, erythema, and pain are also produced by venom alone and do not by themselves establish infection. Reported complications include cellulitis, necrotizing fasciitis, and, rarely, mediastinitis.

Cellulitis is a common complication after snakebites, presenting with swelling, redness, and pain at the bite site. It was seen in a substantial proportion of patients across studies, underscoring both its frequency and the need for effective management approaches [10,11].

Necrotizing fasciitis is a further life-threatening infection that may spread beyond the bite site to regions such as the neck and chest, potentially resulting in mediastinitis. Management typically requires prompt surgical debridement and antibiotic therapy [12].

Compartment syndrome is often linked to severe limb swelling and increased intra-compartmental pressure; it may require surgical intervention to avert permanent damage. Although soft-tissue infections following snake envenomation present major clinical challenges, improvements in surgical and antibiotic treatments have enhanced patient outcomes. Nonetheless, persistent disparities in healthcare access and the quality of emergency assessment, particularly in rural settings, continue to influence clinical management and patient outcomes, underscoring the need for further research.

Whether venom-induced consumption coagulopathy (VICC) is related to the severity of local soft-tissue injury is uncertain. Rajkumar et al. [13] suggested that severe cellulitis of the bitten limb may indicate a reduced VICC risk, which runs against the intuitive expectation that a larger venom dose produces both worse coagulopathy and worse local injury. Clarifying this relationship could help early risk assessment in emergency care, provided it is interpreted correctly.

VICC, local venom-induced tissue injury, and secondary bacterial infection are related but distinct processes. VICC is a systemic process in which procoagulant venom toxins activate the clotting cascade and consume fibrinogen and clotting factors, generating fibrin degradation products such as D-dimer. Local tissue injury results from the direct cytotoxic, myotoxic, and proteolytic effects of venom together with inflammatory mediator release and increased capillary permeability, and it may progress to necrosis or compartment syndrome. Secondary bacterial infection (for example, cellulitis or necrotizing fasciitis) is a later complication that needs evidence beyond swelling and erythema. In this study, local soft-tissue severity was therefore graded clinically as inflammation and tissue injury, and bacterial infection was not diagnosed. There is no established mechanism by which VICC itself damages local tissue. A more plausible reason for the two to occur together is a shared upstream determinant, chiefly the amount and type of venom injected, which was not measured here. The evidence is conflicting: some series link coagulopathy to worse overall

outcomes after snakebite [7], whereas Rajkumar et al. [13] found the opposite pattern for severe cellulitis.

Lacuna in knowledge

There is a notable absence of standardized guidelines for assessing coagulation markers in snakebite patients, particularly those with mild or moderate envenomation. This gap is evident in the study by Moriarity et al. [14], which suggests that routine coagulation tests are necessary for all envenomation cases because of the unpredictability of coagulation abnormalities.

Although VICC is well documented after envenomation by many snake species, the specific relationship between VICC and local soft-tissue injury has not been sufficiently investigated, and the intricate nature of venom constituents, with their varied effects on the coagulation cascade and on tissue integrity, adds to this uncertainty.

Objectives

The objectives of this study were to evaluate the association between baseline VICC markers and the clinical severity of local soft-tissue inflammation (STI) and injury in snakebite patients, and to explore whether these markers predict the need for advanced medical intervention.

Materials And Methods

Study design and setting

This prospective observational study was conducted in the emergency department of the R.L. Jalappa Hospital and Research Centre, a rural, tertiary care teaching hospital located in Tamaka, Kolar, Karnataka, South India. This setting serves a large agricultural population with a high incidence of snakebite envenomation. The clinical data collection and patient follow-up were conducted over a 12-month period between September 2025 and September 2026.

Participant selection and eligibility

All consecutive patients presenting to the emergency department with a history of snakebite and visible localized soft-tissue swelling of the bitten limb were screened for eligibility. The inclusion criteria restricted the cohort to patients aged 18 years and older who presented within 48 hours of the bite and exhibited evidence of localized tissue swelling. Patients were excluded if they met any of the following criteria: a history of pre-existing congenital or acquired bleeding disorders (e.g., hemophilia, Von Willebrand disease, or thrombocytopenia), chronic liver disease, current therapy with immunosuppressive drugs, or current use of antiplatelet agents or anticoagulants such as heparin, warfarin, or direct oral anticoagulants. These criteria were strictly applied to isolate the specific effects of snake envenomation on the human coagulation cascade.

Clinical soft-tissue grading framework

Upon presentation, patients underwent a comprehensive clinical evaluation. Localized STI and swelling on the affected limb were assessed and categorized into four distinct, progressive grades using a grading framework defined by the authors for the purpose of this study, as detailed in Table *1*.

Soft-tissue grade	Clinical presentation and inflammatory signs
Grade I	Symptoms and signs restricted to superficial swelling, mild erythema, warmth, localized lymphadenopathy, and mild pain at the bite site, in the absence of systemic features.
Grade II	Moderate swelling accompanied by systemic signs (e.g., fever, chills, and lymphangitis) or swelling presenting with rapidly advancing edges across joint lines.
Grade III	Severe localized inflammation and swelling characterized by a failure to respond clinically or regress after 48 hours of standard treatment and initial antivenom therapy.
Grade IV	Advanced local tissue envenomation progressing to necrotizing fasciitis, tissue gas formation, or clinical compartment syndrome, or leading directly to septic or toxic shock.

TABLE 1: Soft-tissue inflammation grading as per the study criteria

Study-defined clinical grading system for soft-tissue inflammation in snakebite patients.

Source: The table was developed by the authors specifically for this study and was not adapted from, or based on, any previously published or externally validated grading scale. The four grades were prespecified from the clinical features of local STI and tissue injury observed in snakebite patients (swelling, erythema, lymphangitis, failure to regress after antivenom therapy, necrotizing fasciitis, and compartment syndrome), and Grades III and IV were prespecified as severe soft-tissue involvement. The framework has not been externally validated.

Grading process and timing of assessment

The grade was assigned by the treating emergency physician at the bedside as part of routine clinical care, using the criteria in Table *1*. Features defining Grades I, II, and IV were recorded at presentation (0 hours) and at each clinical review. Grade III requires the response to standard treatment and initial antivenom over 48 hours, so the grade used in the analyses was the highest grade documented during the first 48 hours. Baseline blood samples were taken at 0 hours, before antivenom, and no laboratory value forms part of any grade definition. Grading was not blinded to laboratory results: the grader could see results during routine care, so incorporation or review bias cannot be excluded. Inter-rater reliability was not assessed because grading was done by a single clinician for each patient. The scale is study-defined and has not been validated. Misclassification is likely near the Grade II/III boundary, because Grade II includes systemic signs (fever, chills, and lymphangitis) that may reflect venom effects or infection, and Grade III depends on a treatment response that varies with the timing and dose of antivenom. Defining Grade III by failure to respond to treatment also introduces circularity and classification bias, because patients with a larger venom load are both more likely to fail to respond and more likely to have marked coagulopathy; this would tend to strengthen, not weaken, the observed association. The grades are therefore interpreted only as an ordinal clinical severity category and not as a diagnosis of infection.

Laboratory and coagulation assay protocols

Immediately upon presentation (0 hours) and prior to the administration of any polyvalent anti-snake venom, venous blood samples (2 mL each) were drawn from an uninvolved limb. Parallel bedside evaluations were initiated by putting blood into two clean, dry, ordinary borosilicate glass test tubes kept at room temperature to perform the 20-minute and 30-minute whole blood clotting tests. Bedside 20WBCTs were set up at presentation by placing blood in clean, dry glass tubes at room temperature. These tests were not part of the prespecified analysis: no 20WBCT result is reported, analyzed, or used to define any grade or the endpoint. This study therefore makes no claim about their performance or their comparison with the quantitative laboratory markers. Simultaneously, anticoagulated blood samples collected in sodium citrate vacutainers were transferred to the clinical hematology laboratory for formal automated coagulation profiling.

The automated laboratory panel included the following: prothrombin time (PT) and international normalized ratio (INR) (calculated using a semi-automated coagulation analyzer with a reagent containing thromboplastin and calcium chloride; the normal laboratory reference range was defined as PT < 17 s and INR < 1.2), activated partial thromboplastin time (aPTT) (measuring the intrinsic and common pathways, with a normal reference range of 25-30 s), fibrinogen concentration (quantified via the automated Clauss method, with normal values defined as 200-400 mg/dL), and quantitative D-dimer (assessed via a high-sensitivity automated fluorescence immunoassay, with normal levels defined as <500 ng/mL). These laboratory and bedside markers were repeated at 48 hours post-admission to evaluate the progression or regression of systemic coagulopathy and localized STI.

Primary composite endpoint

The primary prognostic outcome of interest was the clinical requirement for "advanced medical intervention," defined as a composite endpoint comprising the necessity for surgical intervention, including emergency fasciotomy for compartment syndrome, sharp excisional wound debridement of necrotic or gangrenous tissue, or secondary reconstructive surgery (e.g., split-thickness skin grafting); admission to the intensive care unit for hemodynamically unstable shock, severe cardiac arrhythmias, or multiple organ dysfunction syndrome; and the administration of high-dose, repeated polyvalent anti-snake venom (exceeding the standard initial 10 vials) or adjunctive blood products (e.g., fresh frozen plasma, cryoprecipitate, or packed red blood cells) to resolve persistent, refractory systemic envenomation or severe anemia.

The three components were chosen to capture the main forms of advanced care in snakebite: (i) surgical intervention, as a marker of severe local tissue injury; (ii) intensive-care admission, as a marker of systemic instability; and (iii) high-dose antivenom (more than 10 vials) or blood products, as a marker of persistent systemic envenomation and coagulopathy. These components are not equivalent in clinical weight or cause. The third component is partly determined by the coagulation results under study, because clinicians may give further antivenom or plasma on the basis of abnormal clotting tests; this introduces circularity when coagulation markers are used as predictors. Decisions to operate, admit, or transfuse were made by the treating team during routine care, so thresholds may differ between clinicians.

Results

Participants and baseline characteristics

Of 112 consecutive patients enrolled, 104 (92.9%) completed the 48-hour reassessment, and eight (7.1%) were lost to follow-up. Patients lost to follow-up did not differ from those retained in any baseline coagulation index (Mann-Whitney, all $p \geq 0.17$) or in the proportion with local soft-tissue involvement (1/8, 12.5% vs 26/104, 25.0%; Fisher $p = 0.68$), supporting an unbiased complete-case approach for 48-hour endpoints. Baseline analyses use all 112 patients (Table *2*); 48-hour and intervention analyses use the 104 retained.

Parameter	Median (IQR)	Range
PT (s)	15.0 (13.0-17.0)	10-26
INR	1.36 (1.23-1.60)	0.76-2.90
aPTT (s)	39.0 (34.0-47.3)	25-82
Fibrinogen (mg/dL)	248 (163-285)	51-377
D-dimer (ng/mL)	692 (536-1,045)	96-3,924

TABLE 2: Baseline coagulation profile (n = 112)

IQR: interquartile range; PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time

Local STI was graded I in 39 patients (34.8%, 95% confidence interval (CI) 26.6-44.0), II in 46 (41.1%, 32.4-50.3), III in 15 (13.4%, 8.3-20.9), and IV in 12 (10.7%, 6.2-17.8); 27 patients (24.1%, 17.1-32.8) therefore met the prespecified definition of severe local soft-tissue involvement (Grade III/IV). Intensive intervention was required in 23 of 104 retained patients (22.1%, 15.2-31.0). All coagulation indices deviated from normality (Shapiro-Wilk $p < 0.001$), so non-parametric methods and median (interquartile range (IQR)) summaries are used throughout, with Benjamini-Hochberg control of the false discovery rate across the five markers within each analytic family (reported as q). Only 23 outcome events were available, which limits the precision and stability of all prediction estimates reported below.

Coagulation indices and STI severity

All five baseline indices separated severe from non-severe local soft-tissue involvement with very large effect sizes (Table *3*). Fibrinogen was lower and PT, INR, aPTT, and D-dimer higher in severe disease; all comparisons remained significant after false-discovery-rate correction (all $q < 0.001$). Absolute rank-biserial correlations ranged from 0.80 to 1.00, indicating near-complete or complete stochastic dominance between strata. These effect sizes should be interpreted cautiously: they derive from 27 patients with severe disease, from a study-defined and non-validated grade, and from a tertiary referral population in which intermediate presentations may be under-represented.

Marker	Severe (III/IV) n = 27	Non-severe (I/II) n = 85	Rank-biserial r	q (BH)
PT (s)	21.0 (18.5-23.5)	14.0 (13.0-15.0)	+0.80	<0.001
INR	2.20 (1.70-2.30)	1.30 (1.20-1.40)	+0.91	<0.001
aPTT (s)	53.0 (49.5-65.5)	37.0 (33.0-41.0)	+0.88	<0.001
Fibrinogen (mg/dL)	132 (113-151)	264 (241-297)	−0.97	<0.001
D-dimer (ng/mL)	2,717 (2,230-3,266)	619 (503-749)	+1.00	<0.001

TABLE 3: Baseline coagulation indices by soft-tissue inflammation stratum

Mann-Whitney U test; q: Benjamini-Hochberg (BH) adjusted p across five markers. A rank-biserial r of +1.00 for D-dimer denotes complete separation (no overlap between strata), addressed below.

PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time

Absence of a graded dose response across STI grades

Because the ordinal grade is the clinically meaningful exposure, association with grade was examined directly rather than inferred from the dichotomized stratum. Although Spearman correlations with grade were moderate and significant (ρ = +0.45 to +0.53 for PT, INR, aPTT, and D-dimer; ρ = −0.58 for fibrinogen; all q < 0.001), this apparent gradient was attributable entirely to the step between Grade II and Grade III. No index differed between Grade I and Grade II (all p ⩾ 0.11) or between Grade III and Grade IV (all p ⩾ 0.38, except aPTT, p = 0.028, in which Grade IV values were paradoxically lower than Grade III). Within-stratum correlations with grade were null or inverse (non-severe ρ = −0.17 to −0.04; severe ρ = −0.44 to +0.18). Coagulation derangement therefore behaves as a threshold phenomenon distinguishing severe from non-severe disease, not as a continuous correlate of increasing grade (Figure *1*). Ordinal correlation coefficients should not be interpreted as evidence of a dose-response relationship in this cohort.

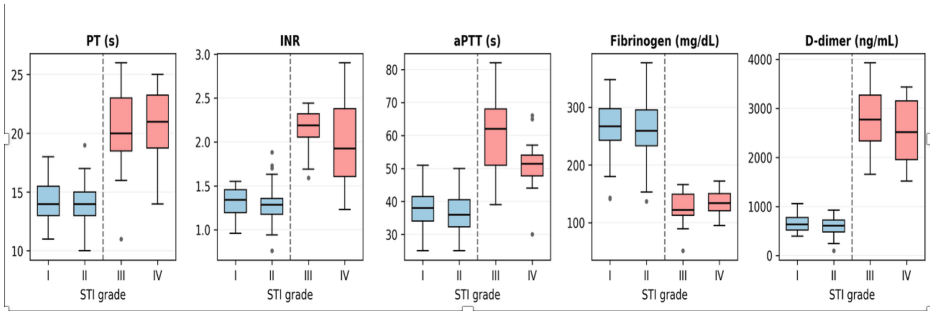


FIGURE 1: Baseline coagulation indices by STI grades

Distribution of baseline coagulation indices across STI Grades I-IV (n = 112). Boxes show median and interquartile range (IQR); whiskers extend to 1.5 × IQR. The dashed line marks the Grade II/III boundary. Values are essentially indistinguishable within the non-severe (I-II) and severe (III-IV) strata, with an abrupt step at the boundary, indicating threshold rather than graded behavior.

PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; STI: soft-tissue inflammation

Prediction of the need for intensive intervention

Need for intensive intervention was the prespecified clinical endpoint and, unlike the soft-tissue severity stratum, showed overlapping marker distributions between outcome groups, permitting valid discrimination analysis. All five indices discriminated moderately well, with areas under the curve (AUCs) of 0.79-0.83 and overlapping CIs (Table *4*, Figure *2*). INR (AUC 0.825, 95% CI 0.70-0.93) and D-dimer (AUC 0.822, 0.71-0.93) performed best. Pairwise DeLong tests for correlated curves confirmed that no marker was superior to any other (INR vs D-dimer p = 0.97; vs fibrinogen p = 0.73; vs aPTT p = 0.65; vs PT p = 0.64). Because thresholds were selected and evaluated in the same dataset, Youden indices are reported both as apparent values and after bootstrap optimism correction (500 resamples); shrinkage was modest (0.03-0.05), indicating limited but non-trivial overfitting. Negative predictive values (NPVs) were 89.4%-93.6% at the study prevalence of 22.1%, and positive predictive values were 50.0%-73.7%; both are prevalence-dependent and imprecise (95%

CIs in Table 5), and each threshold missed five of the 23 events (nine of 23 for PT). These values are exploratory and do not establish that any threshold can safely rule out the need for intensive intervention. The D-dimer threshold identified here (1,520 ng/mL) coincides with the value separating the soft-tissue severity strata, reflecting the strong but non-deterministic association between baseline stratum and subsequent intervention (69.2% vs 6.4%; odds ratio (OR) 32.9, 95% CI 9.6-112.5); 13 of 104 patients were discordant, so the endpoints are related but not interchangeable. Because the D-dimer threshold of 1,520 ng/mL classified patients exactly as the Grade III/IV stratum did, the D-dimer result for the intervention endpoint is not independent of the grade-based finding; it reflects the same association rather than additional information.

Marker	AUC	95% CI	Cut-off	Sens %	Spec %	J apparent	J corrected	q (BH)
INR	0.825	0.70-0.93	≥1.6	78.3	87.7	0.659	0.633	<0.001
D-dimer (ng/mL)	0.822	0.71-0.93	≥1,520	78.3	90.1	0.684	0.648	<0.001
Fibrinogen (mg/dL)	0.807	0.69-0.91	≤172	78.3	84.0	0.622	0.580	<0.001
aPTT (s)	0.798	0.67-0.91	≥44	78.3	77.8	0.560	0.507	<0.001
PT (s)	0.794	0.68-0.89	≥19	60.9	93.8	0.547	0.516	<0.001

TABLE 4: Discrimination for need for intensive intervention (n = 104, 23 events)

AUC 95% CI by percentile bootstrap (2,000 resamples). Cut-offs by Youden index. J corrected = optimism-corrected Youden index (Harrell bootstrap, 500 resamples). Sensitivity and specificity are apparent values and are optimistically biased.

AUC: area under the curve; CI: confidence interval; BH: Benjamini-Hochberg; INR: international normalized ratio; aPTT: activated partial thromboplastin time; PT: prothrombin time

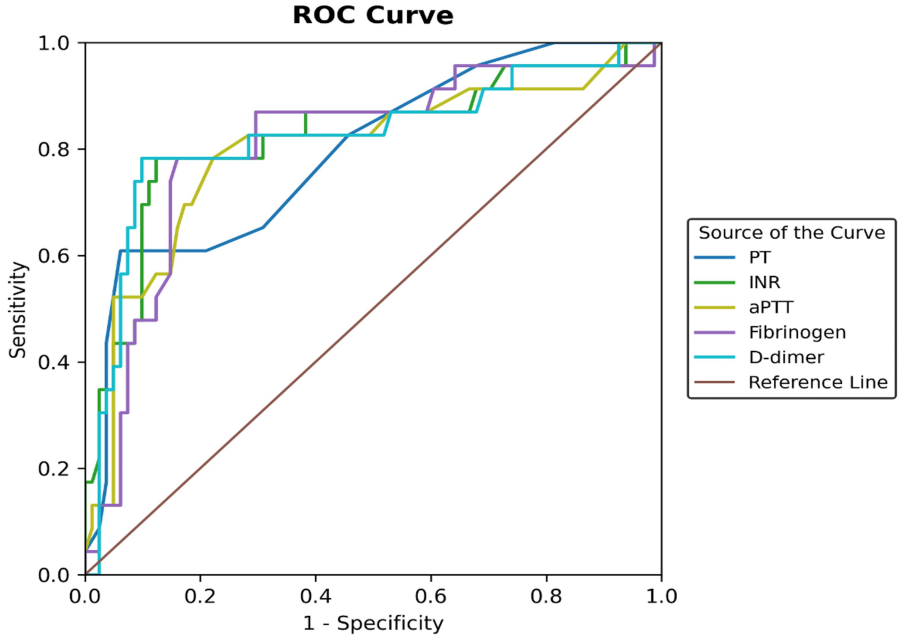


FIGURE 2: Baseline coagulation indices for the prediction of need for intensive intervention

Receiver-operating-characteristic (ROC) curves of baseline coagulation indices for the prediction of need for intensive intervention (n = 104, 23 events). Fibrinogen is reverse-scored so that higher values denote greater risk, allowing all curves to share a common positive-test direction.

INR: international normalized ratio; aPTT: activated partial thromboplastin time; PT: prothrombin time

Marker (cut-off)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
INR ≥ 1.6	78.3 (58.1-90.3)	87.7 (78.7-93.2)	64.3 (45.8-79.3)	93.4 (85.5-97.2)
D-dimer ≥ 1,520 ng/mL	78.3 (58.1-90.3)	90.1 (81.7-94.9)	69.2 (50.0-83.5)	93.6 (85.9-97.2)
Fibrinogen ≤ 172 mg/dL	78.3 (58.1-90.3)	84.0 (74.5-90.4)	58.1 (40.8-73.6)	93.2 (84.9-97.0)
aPTT ≥ 44 s	78.3 (58.1-90.3)	77.8 (67.6-85.5)	50.0 (34.5-65.5)	92.6 (83.9-96.8)
PT ≥ 19 s	60.9 (40.8-77.8)	93.8 (86.4-97.3)	73.7 (51.2-88.2)	89.4 (81.1-94.3)

TABLE 5: Sensitivity, specificity, and predictive values of the cut-offs in Table 4, with 95% CIs (n = 104; 23 events, 81 non-events)

INR: international normalized ratio; aPTT: activated partial thromboplastin time; PT: prothrombin time; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value

Cell counts were reconstructed from the sensitivities, specificities, and event numbers in Table *4* and reproduce the reported predictive values exactly. Wilson score intervals. At the study prevalence, about one in 15 patients classified as low risk would still have an event by point estimate (NPV about 93%), and as many as about one in seven at the lower confidence limits (NPV 84%-86%; 81% for PT).

Complete separation for the STI stratum

Discrimination for the severe STI stratum could not be validly quantified. Baseline D-dimer separated the strata completely: the maximum value among non-severe patients was 1,055 ng/mL and the minimum among severe patients 1,520 ng/mL, with no patient in the intervening 465 ng/mL interval. The resulting AUC of 1.000 and the apparent optimal threshold of 1,520 ng/mL, which coincides exactly with the minimum observed severe value, are artefacts of this separation rather than estimable performance; CIs are degenerate, and the maximum-likelihood OR is undefined. Fibrinogen showed quasi-complete separation, with only 15 of 112 observations in the overlapping range. Accordingly, discrimination statistics for the severe STI stratum are not reported, and associations are presented instead as Firth penalized ORs (Table *6*), which remain finite under separation. These estimates are substantially smaller than the corresponding unpenalized maximum-likelihood values (for example, INR 27.3 vs 39.5 per standard deviation), confirming that conventional logistic regression is inflated in this setting. The D-dimer estimate remains uninterpretable, with a CI spanning four orders of magnitude.

Marker (per 1 SD)	Firth OR	95% CI
PT	11.5	5.0-36
INR	27.3	8.1-195
aPTT	28.2	8.3-154
Fibrinogen	0.01	<0.001-0.05
D-dimer	2,840	69.7-6.4 × 10^8

TABLE 6: Firth penalized logistic regression for severe soft-tissue inflammation (n = 112, 27 events)

Firth penalization applied because of complete (D-dimer) and quasi-complete (fibrinogen, INR, and aPTT) separation. Confidence intervals (CIs) are profile penalized-likelihood intervals, which remain valid under separation, rather than Wald intervals. The D-dimer estimate is reported for completeness only and should not be interpreted.

PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; SD: standard deviation; OR: odds ratio

Multivariable analysis

A multivariable model for need for intervention included INR, D-dimer, and fibrinogen, the three markers with the highest univariable discrimination. Collinearity was acceptable (variance inflation factors 2.2-3.0; pairwise Spearman |ρ| 0.46-0.57). With 23 events and three predictors, the model contained 7.7 events per

variable, below the conventional threshold of 10, and estimates should be regarded as unstable. No marker retained independent significance: adjusted ORs per standard deviation were 2.30 for D-dimer (95% CI 0.98-5.40, p = 0.057), 1.63 for INR (0.80-3.32, p = 0.18), and 0.78 for fibrinogen (0.33-1.88, p = 0.59); McFadden pseudo-R^2 was 0.32. The data do not support selection of any single marker over the others.

Evolution of coagulation and soft-tissue findings at 48 hours

Among the 104 patients reassessed, all indices moved toward reference ranges by 48 hours (Wilcoxon signed-rank, all q < 0.001): median PT fell from 15.0 to 12.0 s, INR from 1.36 to 1.00, aPTT from 39.0 to 29.5 s, and D-dimer from 698 to 427 ng/mL, while fibrinogen rose from 247 to 328 mg/dL. Matched-pairs rank-biserial correlations were −1.00 for PT, −0.99 for INR, −0.97 for aPTT, and −0.79 for D-dimer, and +1.00 for fibrinogen, the sign indicating the direction of change; improvement was therefore near-universal rather than confined to a subgroup. Local soft-tissue grade improved by at least one grade in 32 patients (30.8%), was unchanged in 58 (55.8%), and progressed in 14 (13.5%). Because all patients received antivenom and supportive care and no untreated comparator existed, these within-patient changes cannot be attributed to treatment and are reported descriptively. The baseline values quoted here are medians for the 104 retained patients and therefore differ slightly from Table *2* (n = 112).

Discussion

In this single-center observational cohort, severe local soft-tissue involvement (Grade III/IV) was associated with more marked abnormalities in baseline coagulation indices, particularly higher D-dimer and lower fibrinogen, but the association was categorical rather than graded. VICC, a systemic consumptive process, and local venom-induced tissue injury are distinct processes, and this study cannot establish that one causes the other. A more plausible explanation is that both reflect a common determinant, most likely the amount of venom injected (and possibly the species and the delay to treatment), none of which was measured. The association is consistent with reports that coagulopathy is linked with worse outcomes after snakebite [7]. Rajkumar et al. [13], in contrast, suggested that severe cellulitis of the bitten limb may indicate a reduced VICC risk. Our findings point in the opposite direction. Plausible reasons for the discrepancy include differences in how local severity was defined (venom-induced injury and inflammation here, cellulitis there), the timing of assessment, the species involved, and the study population, but our data cannot resolve this, and the two sets of findings should be regarded as unreconciled.

We did not study mechanisms, and our data do not show that local defenses are “exceeded” or that the coagulation system “passes a critical threshold.” The step between Grade II and Grade III may partly reflect the way the scale is built: Grade III is defined by non-response to antivenom at 48 hours, which is more likely when the venom load is high, or treatment is delayed, and the same factors would raise D-dimer and lower fibrinogen. The “threshold” is therefore a descriptive feature of this dataset and may be partly an artefact of the grading definition, the small number of severe cases (n = 27), and the spectrum of patients at a referral center.

A central insight from this research is the presence of a threshold effect that differentiates non-severe (Grade I/II) disease from severe (Grade III/IV) disease. Coagulation markers were virtually the same in patients with Grade I and Grade II envenomation, indicating that moderate local swelling (Grade II) does not necessarily translate into a proportional rise in systemic risk relative to mild cases. This is in keeping with Moriarity et al. [14], who found that coagulation abnormalities are unpredictable even in apparently mild envenomations and therefore advocated routine coagulation testing; in our cohort, the median baseline INR in non-severe patients (1.30) was already above the laboratory reference limit (1.2). The step in marker levels between Grade II and Grade III is a descriptive finding; because patients were not followed serially in a way that would show individual patients crossing a threshold, it should not be taken to mean that a patient’s condition changes abruptly once a biological threshold is crossed. The NPVs of INR and D-dimer (93.4% and 93.6%; 95% CIs 85.5%-97.2% and 85.9%-97.2%) are based on only 23 events in a single center, and about one in seven patients below the threshold could still need intervention at the lower confidence limit. They are not sufficient to support using these markers to rule out intensive intervention and require external validation before any clinical use. The value of D-dimer is further supported by Isbister et al. [15], who showed that quantitative D-dimer is an accurate early marker of VICC in Australian snakebite patients. The cut-off they proposed (2.5 mg/L) was derived to diagnose VICC rather than to predict the need for intervention, and in a different setting, so it cannot be compared directly with the threshold identified here (1,520 ng/mL). Because the 20WBCT has variable sensitivity [8,9], quantitative laboratory markers such as those evaluated here may add value where laboratory facilities are available.

The data suggest a possible “refractory” subgroup, particularly among Grade III patients; however, Grade III is itself defined by non-response to treatment at 48 hours, so this description is partly circular. These patients are characterized by a lack of response to standard therapy and the initial antivenom within 48 hours. In this cohort, this group was characterized by substantial systemic coagulopathy, evidenced by a median D-dimer level of 2,717 ng/mL versus 619 ng/mL in non-severe cases. Patients in this group frequently needed intensive measures, such as repeated high-dose polyvalent anti-snake venom (more than 10 vials) or additional blood products, to manage ongoing envenomation. The near-universal normalization of coagulation indices by 48 hours in our cohort is consistent with the time course described for Russell's

viper coagulopathy by Isbister et al. [16], who also found that the severity of clotting abnormalities was related to venom concentration. The refractory group in our cohort may therefore reflect a greater venom burden, although venom concentrations were not measured in this study. Overall, these observations suggest, but do not show, that patients with marked coagulopathy and severe local involvement may be more likely to need intensive care. Because venom burden was not measured and the endpoint partly depends on coagulation results, we cannot conclude that the disease is "treatment-resistant" or that more aggressive management would change outcomes.

Progression to Grade IV envenomation, characterized by clinical compartment syndrome and necrotizing fasciitis, poses a major surgical challenge. Surgical measures such as emergency fasciotomy and sharp excisional debridement may be required to avert permanent injury or death, and a multidisciplinary approach has been associated with improved outcomes in severe snakebite injuries [11,12]. However, surgery may be complicated by concurrent systemic coagulopathy. Venom-induced swelling can also mimic compartment syndrome without a true rise in compartment pressure, so fasciotomy should not be based on limb swelling alone [17]. In our cohort, the markers associated with the composite outcome (for example, INR ⩾ 1.6 or D-dimer ⩾ 1,520 ng/mL) overlapped with the Grade III/IV stratum. The 20WBCT was set up at presentation but was not analyzed in this study, so we cannot say how the quantitative markers compare with it. A head-to-head comparison would be useful in future work. We did not measure bleeding complications or surgical outcomes, so we cannot say that these markers identify patients at high risk of hemorrhage. Coagulopathy may create a dilemma in which the urgency of surgical tissue salvage must be weighed against the risk of bleeding, although this was not studied directly here. Decisions about fasciotomy should rest on clinical assessment, compartment pressure measurement where available, and specialist input, and not on the thresholds reported in this study. A recent fatal case of suspected compartment syndrome illustrates this dilemma: fasciotomy was deferred because of uncorrected consumption coagulopathy and refractory shock [18].

Limitations

This was a single-center observational study in a rural tertiary hospital, and the findings may not generalize to other settings, snake species, or earlier presentations. (1) Only 23 outcome events and 27 patients in the severe stratum were available, so estimates are imprecise, and the multivariable model (7.7 events per variable) is unstable. (2) The grading scale is study-defined and unvalidated. Grading was not blinded to laboratory results, inter-rater reliability was not assessed, and misclassification near the Grade II/III boundary is likely. (3) Grade III is defined by failure to respond to treatment, which introduces circularity and classification bias that probably inflate the association between coagulation markers and severity. (4) The composite endpoint is heterogeneous and partly influenced by coagulation results, which introduces circularity. (5) Complete separation of D-dimer between severity strata prevented a valid estimate of discrimination. (6) Venom concentration was not measured, and the snake species and bite-to-presentation delay were not analyzed as covariates, so confounding by venom burden cannot be excluded. (7) Cut-offs were derived and assessed in the same dataset, so apparent performance is optimistic despite bootstrap correction, and there was no external validation. (8) Eight patients (7.1%) were lost to follow-up. (9) All patients received antivenom and supportive care, so changes at 48 hours cannot be attributed to treatment. (10) Bacterial infection was not assessed with cultures or inflammatory markers, so the grades describe inflammation and injury and not infection. (11) Bedside whole-blood clotting tests were performed but not analyzed, so the quantitative markers could not be compared with them.

Conclusions

In this single-center prospective observational study of 112 snakebite patients, baseline coagulation indices differed markedly between patients with severe (Grade III/IV) and non-severe (Grade I/II) local soft-tissue involvement but did not differ meaningfully between Grades I and II or between Grades III and IV. The association was therefore categorical and not graded, and the step between Grade II and Grade III accounted for all of the ordinal associations observed. This is an association between a systemic coagulation abnormality and a clinical grade of local inflammation and injury; it does not show that coagulopathy causes local tissue damage, and a shared determinant such as venom burden, which was not measured, may explain both. Bacterial infection was not assessed. The D-dimer separation between strata was complete in this sample, which prevented a valid estimate of discrimination, and the AUC of 1.000 should not be regarded as evidence of perfect predictive performance.

For the need for advanced medical intervention (a heterogeneous composite endpoint with 23 events among 104 patients), PT, INR, aPTT, fibrinogen, and D-dimer discriminated moderately and equivalently (AUC 0.79-0.83, with wide CIs), and no marker was independently predictive in the multivariable model. NPVs of 89.4%-93.6% (lower 95% confidence limits 81%-86%) rest on a small number of events and are not sufficient to support using these markers to rule out intensive intervention. These findings derive from a single tertiary center, from patients with established soft-tissue involvement, and use a study-defined grading scale that has not been validated and a composite endpoint that is partly influenced by coagulation results; they may not extend to other settings, snake species, or earlier presentations. The results are hypothesis-generating. External validation in an independent cohort, with laboratory-blinded grading, standardized endpoint definitions, and measurement of venom burden, is required before any threshold reported here is

used to guide clinical care.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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